

Anephrogenic phenotype induced by SALL1 gene knockout in pigs.

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Public Summary:

Organ transplantation is among the most effective treatments to improve quality-of-life (QOL) in patients with end-stage renal disease (ESRD). However, a chronic shortage of donor kidneys leaves many patients with ESRD no choice, but to undergo continued dialysis treatment, associated with poor QOL, high medical costs and risk of complications. To combat organ shortage in transplantation medicine, a novel strategy has been proposed to generate human organs from exogenous pluripotent stem cells utilizing the developmental mechanisms of pig embryos/foetuses. Genetically modified pigs missing specific organs are key elements in this strategy. In this study, we demonstrate the feasibility of using a genome-editing approach to generate anephrogenic foetuses in a genetically engineered pig model. SALL1 knockout (KO) was successfully induced by injecting genome-editing molecules into the cytoplasm of pig zygotes, which generated the anephrogenic phenotype. Extinguished SALL1 expression and marked dysgenesis of nephron structures were observed in the rudimentary kidney tissue of SALL1-KO foetuses. Biallelic KO mutations of the target gene induced nephrogenic defects; however, biallelic mutations involving small in-frame deletions did not induce the anephrogenic phenotype. Through production of F1 progeny from mutant founder pigs, we identified mutations that could reliably induce the anephrogenic phenotype and hence established a line of fertile SALL1-mutant pigs. Our study lays important technical groundwork for the realization of human kidney regeneration through the use of an empty developmental niche in pig foetuses.

Scientific Abstract:

To combat organ shortage in transplantation medicine, a novel strategy has been proposed to generate human organs from exogenous pluripotent stem cells utilizing the developmental mechanisms of pig embryos/foetuses. Genetically modified pigs missing specific organs are key elements in this strategy. In this study, we demonstrate the feasibility of using a genome-editing approach to generate anephrogenic foetuses in a genetically engineered pig model. SALL1 knockout (KO) was successfully induced by injecting genome-editing molecules into the cytoplasm of pig zygotes, which generated the anephrogenic phenotype. Extinguished SALL1 expression and marked dysgenesis of nephron structures were observed in the rudimentary kidney tissue of SALL1-KO foetuses. Biallelic KO mutations of the target gene induced nephrogenic defects; however, biallelic mutations involving small in-frame deletions did not induce the anephrogenic phenotype. Through production of F1 progeny from mutant founder pigs, we identified mutations that could reliably induce the anephrogenic phenotype and hence established a line of fertile SALL1-mutant pigs. Our study lays important technical groundwork for the realization of human kidney regeneration through the use of an empty developmental niche in pig foetuses.

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